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Clinical Practice Guidelines

Type 2 Diabetes in Children and Adolescents

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Constadina Panagiotopoulos MD, FRCPC, Michael C. Riddell PhD, Elizabeth A.C. Sellers MD, FRCPC

KEY MESSAGES

- Anticipatory guidance regarding healthy eating and active lifestyle is recommended to prevent obesity.
- Regular targeted screening for type 2 diabetes is recommended in children at risk.
- Children with type 2 diabetes should receive care in consultation with an interdisciplinary pediatric diabetes healthcare team.
- Early screening, intervention and optimization of glycemic control are essential, as the onset of type 2 diabetes during childhood is associated with severe and early onset of microvascular complications.

Note: Unless otherwise specified, the term "child" is used for individuals 0 to 18 years of age, and the term "adolescent" for those 13 to 18 years of age.

Introduction

Type 2 diabetes in children has increased in frequency around the world over the past 2 decades (1). Children from ethnic groups at high risk for type 2 diabetes in their adult populations, namely, those of Aboriginal, African, Arabic, Hispanic or Asian descent, are disproportionally affected. A recent Canadian national surveillance study demonstrated a minimum incidence of type 2 diabetes in children and adolescents <18 years of age of 1.54 per 100 000 children per year (2). Significant regional variation was observed with the highest minimum incidence seen in Manitoba of 12.45 per 100 000 children per year. In this study, 44% of children with new onset type 2 diabetes were of Aboriginal heritage, 25% Caucasian, 10.1% Asian, 10.1% African/Caribbean and the remaining of other or mixed ethnic origin (2). Recent data from the United States (US) demonstrated an incidence of 8.1 per 100 000 person years in the 10- to 14-year age group and 11.8 per 100 000 person years in the 15- to 19-year group. In this study, the highest rates were found in American Indian, African American, Asian/Pacific Islander and Hispanic youth (in descending order), and the lowest incidence occurred in non-Hispanic white youth (3).

Prevention

Breastfeeding has been shown to reduce the risk of youth-onset type 2 diabetes in some populations (4).

Obesity is a major modifiable risk factor for the development of type 2 diabetes (2). In 2004, 18% of Canadian children and adolescents were overweight and 8% were obese (5). Studies on the prevention of obesity in children are limited and have generally not been demonstrated to be successful (6). In obese children, standard lifestyle interventions in the form of dietary recommendations and regular clinic visits have been shown to have little benefit for weight reduction (6). While data are limited, family-based lifestyle interventions with a behavioural component aimed at changes in diet and physical activity patterns have been shown to result in significant weight reduction in both children and adolescents (6). Health Canada–endorsed recommendations for physical activity and nutrition in children can be accessed on the Canadian Society for Exercise Physiology (http://www.csep.ca/english/view.asp?x=804) and Health Canada (http://www.hc-sc.gc.ca/fn-an/food-guide-aliment/choose-choix/advice-conseil/child-enfant-eng.php) websites (7,8).

The role of pharmacotherapy in the treatment of childhood obesity is controversial, as there are few controlled trials and no long-term safety or efficacy data (9). Several studies suggest that lifestyle changes plus pharmacotherapy may act synergistically when lifestyle intervention is aggressively pursued (10). Orlistat may be considered to aid in weight reduction and weight maintenance when added to a regimen of lifestyle intervention in adolescents (11–13). Metformin has been observed to promote modest weight loss in small, short-term trials in children and adolescents (9). However, while both metformin and orlistat have potential for short-term positive effects on weight, glycemic control, insulin sensitivity and/or lipids, no pediatric studies have been performed to assess the prevention of diabetes or long-term complications. In obese adolescents with evidence of severe insulin resistance, pharmacological therapy with metformin or orlistat should only be considered after a comprehensive evaluation of the child's metabolic status, family history and review of lifestyle interventions. Due to a lack of data in prepubertal children, the use of antiobesity drugs should only be considered in this population within the context of a supervised clinical trial. Bariatric surgery in adolescents should be limited to exceptional cases and be performed only by experienced teams (14).

Screening and Diagnosis

The microvascular complications of type 2 diabetes have been identified at diagnosis, implying long-term, unrecognized

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at diagnosis (40). In addition, psychological issues, such as depression, binge eating (41) and smoking cessation, need to be addressed and interventions offered as required. In 1 retrospective cohort of pediatric patients, the prevalence of neuropsychiatric disorders at presentation of type 2 diabetes was 19.4% (26).

Insulin is required in those with severe metabolic decompensation at diagnosis (e.g. DKA, glycated hemoglobin [A1C] ≥9.0%, symptoms of severe hyperglycemia) but may be successfully weaned once glycemic targets are achieved, particularly if lifestyle changes are effectively adopted (42). There are limited data about the safety or efficacy of oral antihyperglycemic agents in the pediatric population, and none of the oral antidiabetic agents have been approved by Health Canada for use in children. Metformin has been shown to be safe in adolescents for up to 16 weeks, reducing A1C by 1.0% to 2.0% and lowering FPG with similar side effects as seen in adults (43). Glimepiride has also been shown to be safe and effective in adolescents for up to 24 weeks, reducing A1C (−0.54%) to a similar extent as metformin (−0.71%) but resulting in a significant weight increase of 1.3 kg (44). The Treatment Options for Type 2 Diabetes in Youth (TODAY) study was a multicentre trial that randomized youth with type 2 diabetes to metformin alone, metformin plus a lifestyle intervention, or metformin plus rosiglitazone (45). The study population included youth 10 to 17 years of age with a mean diabetes duration of 7.8 months and A1C <8%. In the entire study population, treatment failure (defined as A1C ≥8% over 6 months or sustained metabolic decompensation requiring insulin therapy) occurred in 51.7% of the metformin group, 46.6% of the metformin plus lifestyle group, and 38.6% of the metformin plus rosiglitazone group (metformin-rosiglitazone vs. metformin alone; p=0.006). However, there were important differences in response between genders and ethnic groups. This study demonstrated that a significant proportion of youth with type 2 diabetes requires aggressive intervention early in the course of the disease, and treatment failure is common. Serious adverse events thought to be related to study medication were uncommon over mean follow-up of 3.9 years. Given the concerns raised around the long-term safety of rosiglitazone since the start of this trial, it is premature to recommend its routine use in children on the basis of this study. A pharmacokinetic and safety study of a single injection of exenatide in 13 adolescents being treated with metformin demonstrated good tolerability and improved postprandial glucose levels (46).

The experience of bariatric surgery in adolescents with type 2 diabetes is very limited with specific eligibility criteria (BMI >35 kg/m^2, Tanner stage IV or V, and skeletal maturity). A single retrospective case series of 11 postpubertal adolescents with type 2 diabetes who underwent roux-en-Y gastric bypass demonstrated significant improvements in BMI, glycemic control, serum lipid levels and blood pressure (BP) compared to 67 adolescents who were medically managed over 1 year (47). Notably, 10 of the 11 surgically treated youth experienced remission of their diabetes without the need for medication.

Immunization

The recommendations for influenza and pneumococcal immunization in Canada do not address the issue of type 2 diabetes in children, and there are no studies evaluating the usefulness of the influenza or pneumococcal vaccine in this population. There is no reason not to manage these children in a similar fashion to those with type 1 diabetes in whom influenza immunization is recommended to be offered as a way to avoid an intercurrent illness that could complicate diabetes management. Some children with type 2 diabetes may also have other factors (e.g. Aboriginal heritage) that may place them at higher risk of increased influenza- and pneumococcal-related morbidity (48–50).

Complications

Short-term complications of type 2 diabetes in children include DKA and hyperglycemic hyperosmolar state (HHS); 10% of Canadian youth present with DKA at the time of diagnosis (2). High mortality rates (up to 37% in 1 series) have been reported in youth presenting with combined DKA and HHS at onset of type 2 diabetes (51–53). Evidence suggests that early-onset type 2 diabetes in adolescence is associated with severe and early-onset microvascular complications, including retinopathy, neuropathy and nephropathy (54–56). Although neither retinopathy nor neuropathy has been described in adolescents with type 2 diabetes at diagnosis, 1 study found that 1 in 5 youth with type 2 diabetes had peripheral nerve abnormalities, and more than half had autonomic neuropathy after a median duration of diabetes of 1.3 years (56). Micro- or macroalbuminuria has been noted in 14.2% of Canadian youth at diagnosis (2) and in up to 22.2% of US youth with a mean diabetes duration of 1.9 years (57). Therefore, it is prudent to consider screening for these complications at diagnosis and yearly thereafter until the natural history is better understood (Table 1). Furthermore, Aboriginal youth in Canada are at increased risk of renal diseases that are not associated with diabetes (58). Given that the documentation of persistent albuminuria may indicate one of several possible diagnoses, including underlying primary renal disease, diabetic nephropathy or focal sclerosing glomerulosclerosis (a comorbid condition associated with obesity), referral to a pediatric nephrologist for assessment of etiology and treatment is recommended (58).

Comorbid Conditions

Children with type 2 diabetes have an increased prevalence of dyslipidemia (56,57,59,60), with 44.8% of Canadian children reported to have dyslipidemia at the time of diagnosis (2). Thus, screening for dyslipidemia at diagnosis and every 1 to 3 years as clinically indicated thereafter is recommended. In children with familial dyslipidemia and a positive family history of early cardiovascular events, a statin should be started if the low-density lipoprotein cholesterol level remains >4.1 mmol/L after a 3- to 6-month trial of dietary intervention (61). A similar approach seems reasonable in the absence of evidence to recommend a specific intervention in children with type 2 diabetes.

Similarly, screening for high BP should begin at diagnosis of diabetes and continue at every diabetes-related clinical encounter thereafter (62), since up to 36% of adolescents with type 2 diabetes have hypertension (56) (see Type 1 Diabetes in Children and Adolescents chapter, p. S153, for additional discussion on the treatment of dyslipidemia and hypertension).

Since 95% of adolescents with type 2 diabetes present with obesity and 73% have clinical evidence of insulin resistance as manifested by acanthosis nigricans (2), surveillance should occur for comorbid conditions associated with insulin resistance, including PCOS (63) and NAFLD (64) (Table 1). PCOS was reported in 12.1% and NAFLD (defined as alanine aminotransferase [ALT] >3× the upper limit of normal or fatty liver on ultrasound) in 22.2% of children and youth at diagnosis of type 2 diabetes (2).

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